REMARKS

Claims 1, 8, 14, and 45-47 are pending in the application. Claims 1 and 46 have been amended. Claims 2-13, and 15-44 have been cancelled. New claim 48 has been added. No new matter has been added by virtue of the amendments, support being found in the specification and in the claims as originally filed. In particular, support for the amendment to claim 1 can be found on page 13, lines 21-30 and on page 50, line 15 to page 51, line 2. Support for new claim 48 can be found in claim 8 as originally filed.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Related Pending Application

Applicants bring U.S. Patent Application No. 10/588,114, titled METHODS FOR MAKING AND USING MOLECULAR SWITCHES INVOLVING CIRCULAR PERMUTATION to the Examiner's attention. U.S. Patent Application No. 10/588,114 was filed by the same inventors as the instant application and is directed to similar subject matter.

Claim Rejections- 35 U.S.C. § 102

The claims stand rejected under 35 U.S.C. § 102 as being anticipated by each of the following: **Lacatena et al.**, 1994 (PNAS, Vol. 91, pp. 10521-10525 "hereinafter "Lacatena"), **Anderson et al.**, U.S. Patent No. 6,596,485 (hereinfter "Anderson"), **Manoil et al.**, 1990 (Journal of Bacteriology, Vol. 172, pp. 515-518; hereinafter "Manoil"), **Mountford et al.**, 1995 (TIG, Vol. 11, No. 5, pp. 179-184; "hereinafter Mountford"), **Ong**, 2005 (U.S. Patent No. 6,867,035; hereinafter "Ong"), and **Heintz et al.**, 2002 (U.S. Patent No. 6,485,912; "hereinafter "Heintz").

Applicants respectfully disagree with the rejections. However, merely to facilitate prosecution, Applicants have amended claim 1. As amended, claim 1 is directed to:

> A method for assembling a modulatable polypeptide, comprising: inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, wherein the insertion sequence encodes a polypeptide that recognizes a first signal and the acceptor sequence encodes a polypeptide that produces a responsive signal provided the responsive signal is not fluorescence, wherein the fused insertion and acceptor sequences encode a modulatable fusion polypeptide having the responsive signal functionally coupled to the first signal.

None of references cited by the Examiner anticipates amended claim 1, because none of the references describes all of the elements of Applicants' invention. For a reference to serve as the basis for an anticipation rejection that reference must disclose each and every element of present in the claim. M.P.E.P. 2131 "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 2001).

Lacatena describes alkaline phosphatase randomly inserted into human beta adrenergic receptor (See Lacatena, Abstract). The alkaline phosphatase domain is active only when it is inserted into a site on the beta adrenergic receptor such that the alkaline phosphatase is exposed to the extracellular environment. Lacatena fails to describes a modulatable polypeptide where the insertion sequence recognizes a first signal and the acceptor sequence produces a responsive signal, wherein the responsive signal is functionally coupled to the first signal. Therefore, Lacatena does not anticipate claim 1.

Anderson describes a GFP protein having random peptide sequences inserted into the GFP, such that the random peptide sequences are conformationally stabilized (See Anderson, Abstract). However, Anderson fails to describe a modulatable polypeptide where the insertion sequence recognizes a first signal and the acceptor sequence produces a responsive signal, where the responsive signal is functionally coupled to the first signal. Moreover, claim 1 is not directed to fluorescent proteins, such as GFP. Therefore, Anderson does not anticipate claim 1.

Manoil describes the use of alkaline phosphatase as a reporter for studies on the topography of hybrid proteins (Manoil, pages 516-517). Manoil teaches that alkaline phosphatase is only active if it is exported across the cytoplasmic membrane into the periplasmic

space (Manoil, Introduction). Manoil fails to describe a modulatable polypeptide, where the insertion sequence recognizes a first signal and the acceptor sequence produces a responsive signal, where the responsive signal is functionally coupled to the first signal. Therefore, Manoil does not anticipate claim 1.

Mountford describes the use of IRES sequences to make dicistronic RNAs in mammalian systems (See e.g., Mountford, Figure 1 on page 180). Mountford fails to describe the production of fusion proteins, but is restricted to making nucleic acid fusions, therefore, Mountford does not anticipate claim 1.

Ong teaches a gene trap vector that is inserted into embryonic stem (ES) cell genomes to both trap genes and simultaneously create mutations in the copy of the gene in the ES cell (See Ong, Abstract). Ong does not teach the production of fusion proteins but is restricted to making nucleic acid fusions, therefore, Ong does not anticipate claim 1.

Heintz describes a gene trapping vector system for gene trapping in BACs (See Heintz, Abstract). Heintz fails to describe the production of fusion proteins, but is restricted to making nucleic acid fusions, therefore, Heintz does not anticipate claim 1.

In sum, none of the cited references, alone or in any combination, describes all of the elements of Applicants' claimed invention.

Claim Rejections- 35 U.S.C. § 103(a)

Claims 1 and 45-47 are rejected under 35 U.S.C. § 103(a) as being obvious over **Anderson et al.**, 2003 (U.S. Patent No. 6,596,485; hereinafter "Anderson") in view of **Norris et al.**, 2006 (U.S. Patent No. 7,135,176; hereinafter "Norris"). Applicants respectfully disagree and traverse the rejection.

However, without acquiescing in any way to the rejection and solely to expedite prosecution, Applicants have amended claim 1. Claim 1 is now directed to a method of assembling modulatable fusion proteins where the insertion sequence encodes a polypeptide domain that recognizes a signal and the acceptor sequence encodes a polypeptide that produces a

responsive signal. The two polypeptides are fused such that when the insertion sequence recognizes a signal the acceptor sequence produces a responsive signal.

The test of obviousness requires that one compare the claimed "subject matter as a whole" with the prior art "to which said subject matter pertains" 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three criteria must be met. First, a suggestion or motivation to modify the reference or combine reference teachings must be present in the references or in the general knowledge present in the art. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. M.P.E.P. 2143. The burden is on the Examiner to show that the references expressly or impliedly suggest all of the claim limitations. M.P.E.P. 2142. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons skilled in the art." *In re Rouffe*t, 149 F.3d 1350, 1357. In the absence of some teaching or suggestion to combine, no *prima facie* case of obviousness can be established, and the rejection is improper and must be withdrawn. *In re Fine*, 837 F.2d 1071, 1074. The references cited by the Examiner fail to provide the requisite motivation to combine; fail to provide a reasonable expectation of success; and fail to teach or suggest all of the claim limitations.

Anderson teaches inserting peptides into GFP such that the peptides are conformationally constrained (See Anderson, Abstract). The peptides are not fused such that GFP produces a responsive signal when the inserted peptide receives a signal. Moreover, claim 1 is not directed to fluorescent proteins. **Norris** fails to cure the deficiencies in Anderson because Norris merely teaches the use of DNase I to randomly insert sequences into bacteriophage DNA (See Norris, col. 48, lines 60-64). Taken together, neither Anderson nor Norris, either alone or in combination, teaches or suggests every Applicants' claimed invention. Therefore, Anderson and Norris do not render the claims obvious.

CONCLUSION

For at least the foregoing reasons, each of the presently pending claims in this application is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be in condition for allowance, the Examiner is requested to call Applicants' undersigned representative to discuss the application. Applicants thanks the Examiner in advance for this courtesy.

The Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105. In view of the foregoing, Applicants request reconsideration and allowance of the pending claims.

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Respectfully submitted,

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